Genetic disorders

- Normal human karyotype
- Pattern of inheritance of genetic disorders
- Mutations
- Disorders with multifactorial inheritance
- Common chromosomal disorders
- Single gene disorders with examples
- Principles of diagnosis of genetic diseases

Genetic disorders

- Genetic disorders are a group of conditions that are caused by changes in a person's dna.
- Dna is the genetic material that carries instructions for building and maintaining an organism.
- Genetic disorders can be caused by changes in single genes, multiple genes or chromosomes.

Normal human karyotype

A karyotype is a picture of a person's chromosomes.

Humans normally have 46 chromosomes, which are arranged in 23 pairs.

Each pair of chromosomes contains one chromosome from the mother and one chromosome from the father.

The first 22 pairs of chromosomes are called autosomes.

The 23rd pair of chromosomes are called sex chromosomes.

Females normally have two X chromosomes, while males normally have one X chromosome and one Y chromosome.

Why karyotyping is significant?

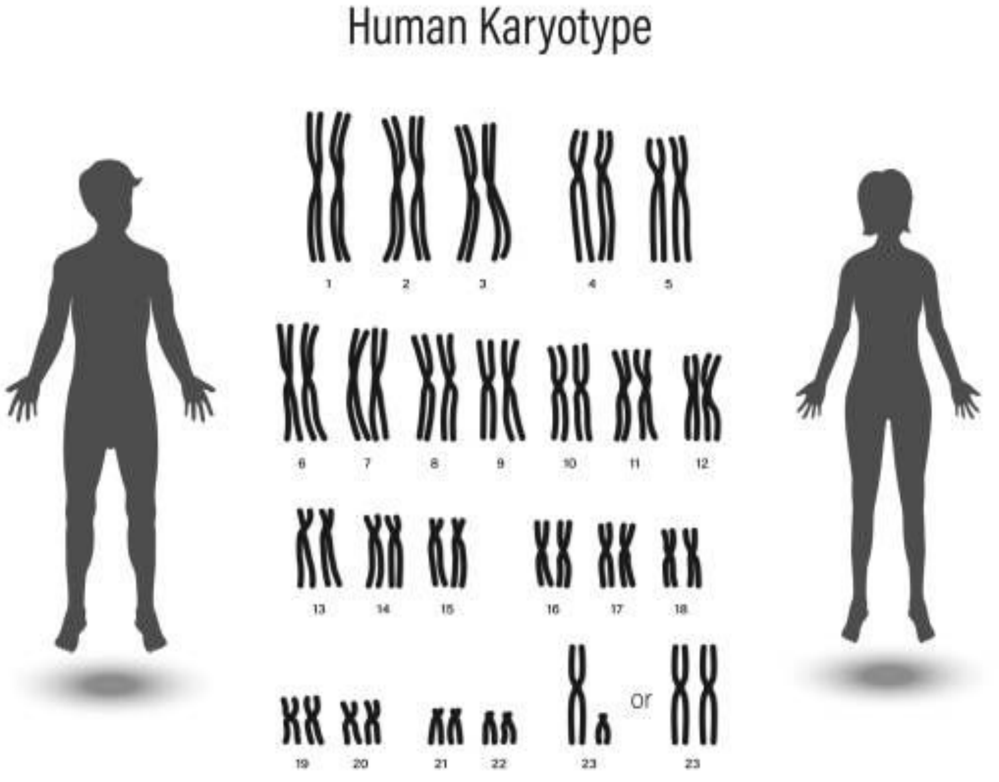
A normal karyotype indicates that a person has the correct number and structure of chromosomes. This is important because changes in the number or structure of chromosomes can lead to genetic disorders.

Karyotypes can be used to diagnose genetic disorders, to determine the sex of a fetus, and to identify individuals who are at risk of passing on a genetic disorder to their children.

However Karyotyping cannot detect all genetic disorders. Some genetic disorders are caused by changes in single genes, which are too small to be seen under a microscope. Other genetic disorders are caused by changes in the DNA that are not visible in the chromosomes.

How a karyotype is prepared

A karyotype is prepared from a sample of cells, such as blood cells.The cells are first treated with chemicals to cause them to divide. The dividing cells are then stained to reveal the chromosomes. The chromosomes are then photographed and arranged in pairs to create a karyotype.



Pattern of inheritance of genetic disorders

The pattern of inheritance simply describes how genetic disorders are passed from the parents to their offspring.
There are four main types of pattern of inheritance;

- Autosomal dominant
- Autosomal recessive
- X Linked dominant
- X Linked recessive

However not all genetic disorders will follow this pattern of inheritance, there are other rare forms of inheritance such as mitochondrial inheritance.

Autosomal dominant inheritance

Disorders of autosomal dominant inheritance are displayed in the heterozygous state, this means that if a person inherits one mutated copy of the gene from one parent and one normal copy from the other parent, they will have the disorder.

- People with autosomal dominant traits or disorders can pass them on to their children, even if the other parent does not have the disorder.
- Both males and females can be affected and both sexes can transmit the condition.
- Some people with autosomal dominant disorders do not have affected parents. This is because the mutation can occur in the egg or sperm cell that forms the child. These children are called **new mutations** and they are the only ones in the family who have the disorder.

Continuation

- Autosomal disorders can be caused by mutations in a variety of genes, and the severity of the disorder can vary depending on the specific gene that is mutated. Some people have mild symptoms while others have severe symptoms that can be life threatening
- There is no cure for autosomal dominant disorders but treatment can help to manage the symptoms

Examples of autosomal disorders

- Huntington's disease
- Achondroplasia (dwarfism)
- Marfan syndrome
- Polydactyly (extra fingers or toes)

Autosomal recessive inheritance

Disorders of autosomal recessive inheritance are manifested in the homozygous state, they occur when both of the alleles at a given gene locus are mutants.Therefore such disorders are characterized by the following features:

- People with one copy of the mutant gene do not usually have the disorder, but they can pass the mutant gene on to their children.
- Each child of two carrier parents has 25% chance of inheriting two copies of the mutant gene and having the disorder
- It's more common in consanguineous marriages (marriages between people who are closely related such as cousins), this is because the parents are more likely to be carriers of the same mutant gene.

Continuation

Most autosomal recessive disorders are caused by mutations in genes that code for enzymes. In carriers of mutant gene, the one normal gene is sufficient for enzyme activity to function properly. But this is not the case for people with the disorder

Example

- Cystic fibrosis an autosomal recessive disorder that is caused by mutation in the gene that codes for the CFTR protein (which helps to regulate salt and water in and out of the cells). People with cystic fibrosis have a defective CFTR protein, which can lead to a buildup of mucus in lungs, pancreas and other organs.
- Sickle cell anaemia, people with this disorder have a defective hemoglobin (a protein that carries oxygen) which cause the red blood cell to take on a crescent shape.

Continuation

Examples of autosomal recessive disorders

- Cystic fibrosis
- Galactosemia
- Phenylketonuria (PKU)
- Sickle cell anaemia
- Tay sachs disease

X-linked dominant pattern of inheritance

X linked dominant inheritance occurs when a mutant gene located on the x chromosome is sufficient to cause a disorder.

Characteristics of x linked dominant inheritance

- Men have one x chromosome hence more likely to be affected than women who have two x chromosomes
- Females with one copy of the mutant gene may also be affected, but their symptoms are less severe than those of males
- The disorder can be passed from affected mother to any of her children, both sons and daughters
- Affected fathers cannot pass the disorder on to their sons

Continuation

Examples of x linked dominant disorders

- Osteogenesis imperfecta(OI)
- Huntington's disease
- Charcot marie tooth disease(CMT)
- Neurofibromatosis type 1(NF1)

X-linked recessive inheritance pattern

X-linked recessive disorders are caused by mutations in both copies of a gene on the X chromosome.

Characteristics of x linked recessive inheritance pattern

- Males are more likely to be affected than females
- Carriers of mutant gene do not show symptoms themselves, but they can pass it to their children
- Affected fathers cannot passthe disorder on to their sons
- The disorder can be passed from an affected mother to any of her sons, but not daughters

Continuation

Examples of x linked recessive disorders

- Colour blindness
- Hemophilia A
- Hunter syndrome
- Duchenne muscular dystrophy
- Menkes syndrome

Mutations

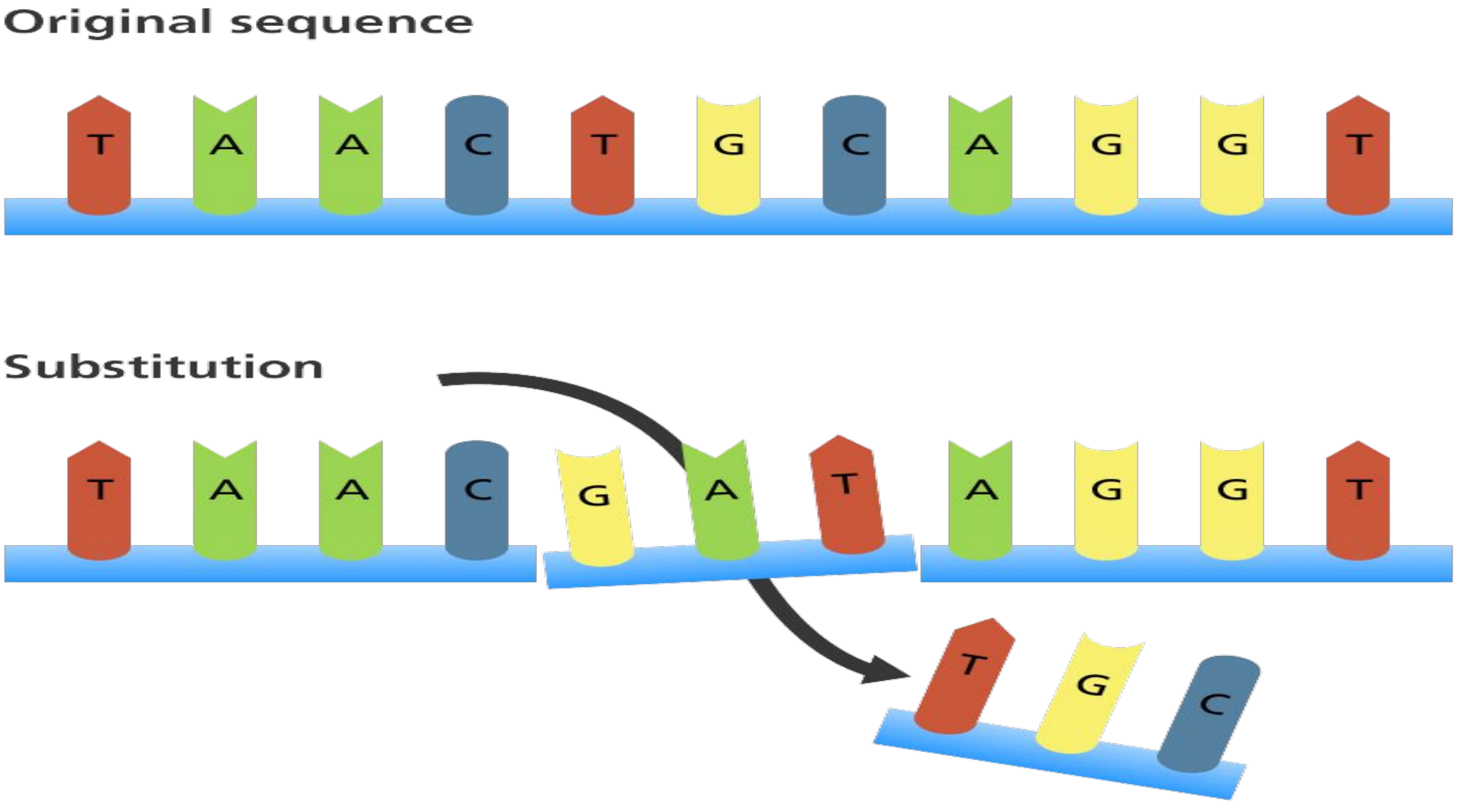
Mutation refer to the permanent changes in DNA. Those that affect germ cells are transmitted to the progeny and may give rise to inherited diseases. Mutations in somatic cells are not transmitted to the progeny but are important in the causation of cancers and some congenital malformations.

Categories of mutation include

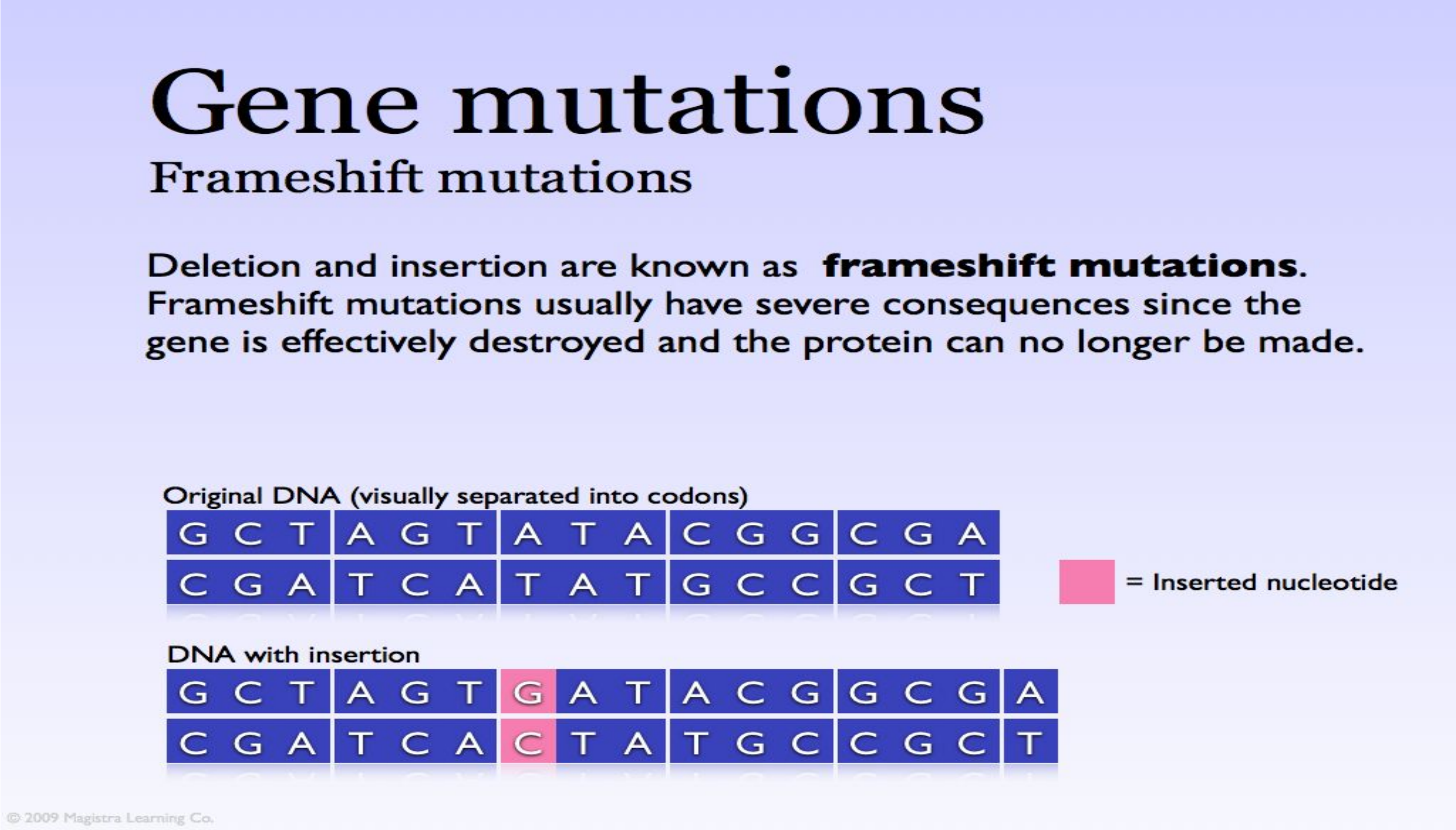
1. **Chromosomal mutation:** Rearranged genetic material giving rise to visible changes in chromosome structure
2. **Gene mutation:** This caused by sub-microscopic changes. some common examples of gene mutations

- **Point mutations;** Result from the substitution of a single nucleotide base by a different base, resulting in the replacement of one amino acid by another in the protein product. **Example of a point mutation :**The mutation in the β-globin chain of haemoglobin giving rise to sickle cell anemia
- **Frameshift mutation:** occurs when the insertion or deletion of one of two base pair alters the reading frame of dna strand
- **trinucleotide repeat mutations:** are a type of genetic mutation characterized by the expansion of a three-nucleotide sequence. These mutations are often associated with neurological disorders, such as fragile X syndrome and Huntington's disease.

Point mutation



Frameshift mutation



Gene mutations

Frameshift mutations

Deletion and insertion are known as **frameshift mutations**. Frameshift mutations usually have severe consequences since the gene is effectively destroyed and the protein can no longer be made.

Original DNA (visually separated into codons)

GCT AGT ATA CGG CGA
CGA TCA TAT GCC GCT

▨ = Inserted nucleotide

DNA with insertion

GCT AGT GAT ACG GCG A
CGA TCA CTA TGC CGC T

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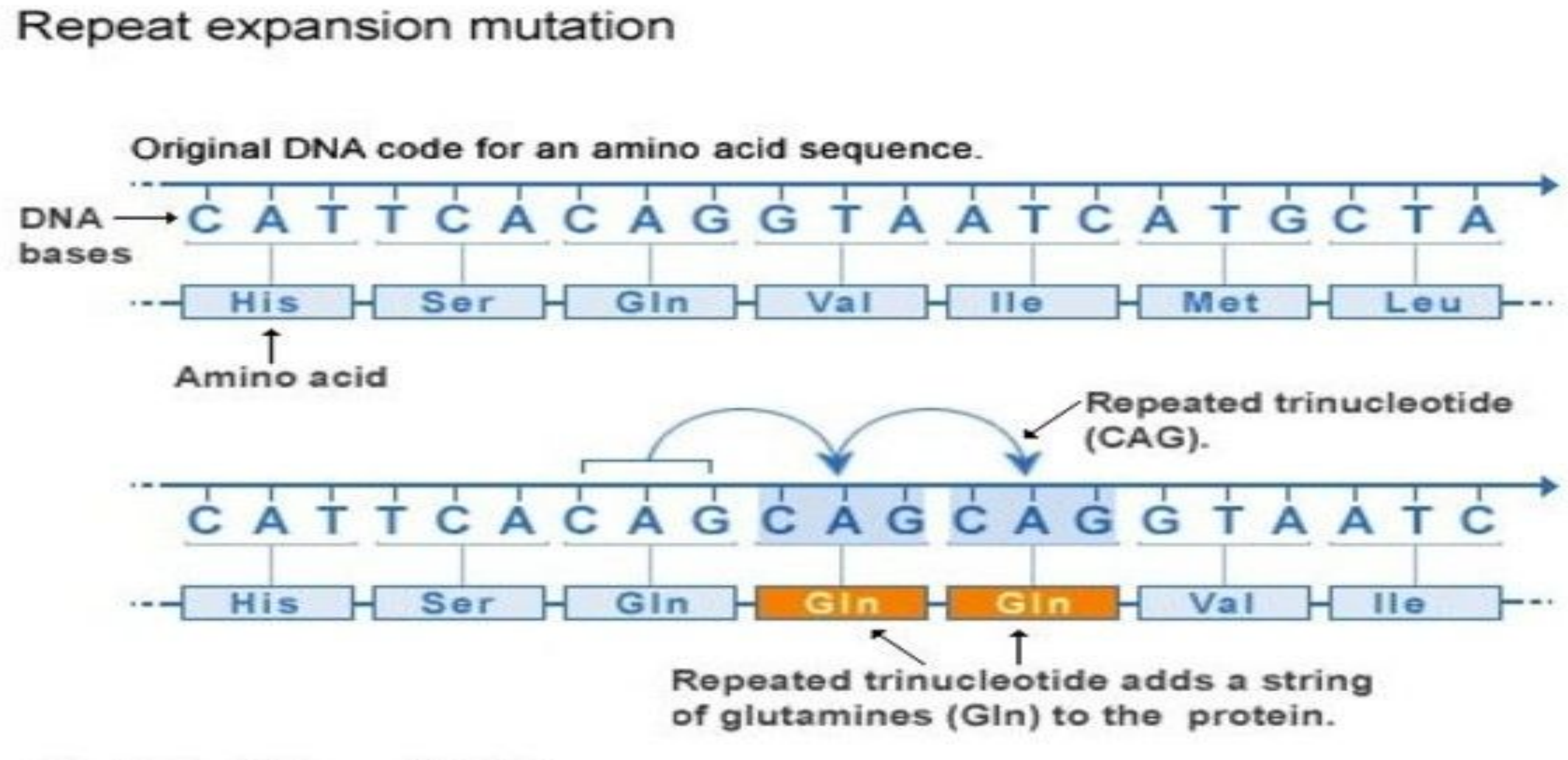
Repeat expansion mutation


Repeat expansion mutation
Original DNA code for an amino acid sequence.
DNA bases
C A T T C A C A G G T A A T C A T G C T A
His
Ser
Gln
Val
Ile
Met
Leu
Amino acid
Repeated trinucleotide (CAG).
C A T T C A C A G C A G C A G G T A A T C
His
Ser
Gln
Gln
Gln
Val
Ile
Repeated trinucleotide adds a string of glutamines (Gln) to the protein.

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Disorders with multifactorial inheritance

Multifactorial inheritance disorder are the conditions that results from a combination of genetic and environmental factors.

They are mostly influenced by multiple genes and environmental factors working together .In multifactorial inheritance none of gene is dominant or recessive to another.

Cont..

Examples of multifactorial inheritance disorders include

- Asthma
- Hypertension
- Autoimmune disorders
- Cancer
- Hypertension
- Intellectual disability
- Diabetes and cleft palate

Asthma

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms,reversible airflow obstruction and bronchospasm.

Asthma is one among multifactorial disorders it may occur due to combination of multiple genes and environmental factors such as pollution, exposure to allergens.

Multiple factors that lead to asthma

Genetic factor; Genetic variation can affect the function of immune system leading to an increased risk of developing allergies, airway responsiveness hence it may lead to asthma.

Environmental factors. Also environmental factor may contribute to asthma example.
Exposure to allergens eg.dust mites,pollen,mold, Pollutants, Tobacco smoke, Respiratory infections, Lifestyle such as diet (It is thought that the inflammation associated with obesity may contribute to the development and worsening of asthma.)

Symptoms and treatment of asthma

Symptoms:

- Difficult breathing due to inflammation and narrowing of airways
- Wheezing. Wheezing is a high-pitched whistling sound that occurs when air moves through narrowed airways in the lungs
- Chest pain,tightness or pressure
- Weakness during sleep
- Difficult in talking

Treatment:

- Medications such as Anti Inflammatory drugs eg. corticosteroid, leukotriene modifiers
- Bronchodilators eg. Beta agonists,Theophylline
- Hygiene

Avoid things that can worsen your asthma

USE U-100 INSULIN ONLY
1 cc
DIABETES

DIABETES

Diabetes is the metabolic disorder characterized by hyperglycemia due to an absolute or relative lack of insulin or cellular resistance to insulin.

Types of Diabetes

1. Type I diabetes/ juvenile diabetes.
2. Type II diabetes

TYPE 1 DIABETES

Type I diabetes is an autoimmune disease in which the body's immune system mistakenly attacks and destroys the insulin-producing cells in the pancreas. This results in a lack of insulin, a hormone that helps glucose enter the cells to be used as energy.

People with type I diabetes require daily insulin injections in order to manage their blood sugar levels.

Cont…

Type II diabetes

Type 2 diabetes, the most common type of diabetes, is a disease that occurs when your blood glucose, also called blood sugar, is too high.

In type 2 diabetes, the body either does not produce enough insulin or becomes resistant to its effects.

Factors affecting diabetes

Environmental factors such as pollution,exposure to certain chemicals and living in high stress environment. Dietary factors such as diet high in processed foods,sugar and unhealthy fat, High blood pressure, Abnormal cholesterol level

SYMPTOMS

- Polyuria
- Polyphagia
- Fatigue
- Delay wound healing
- Skin infections
- Sexual dysfunction
- Numbness in feet and hands

Cont

TREATMENT

- Insulin injection
- Diet
- Exercise
- Glucose monitoring
- Medications eg.Metformin (Fortamet, Glumetza)

COMPLICATIONS

- Retinopathy
- Kidney damage
- Poor blood circulation
- Heart disease and stroke

0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
HYPERTENSION

HYPERTENSION

Hypertension(high blood pressure) is the condition in which arteries have persistently elevated blood pressure greater than normal (120/80mmHg)

MULTIPLE FACTORS THAT CONTRIBUTE TO HYPERTENSION

- Obesity
- High sodium consumption
- Low potassium intake
- Too much alcohol
- Stress

SYMPTOMS

- Headache
- Severe anxiety
- Nosebleeds
- Shortness of breath and Dizziness

TREATMENT

- By consuming health diet.
- By loosing losing weight.
- Lower intake of alcohol.
- Exercise
- Medications such as, ACE inhibitor, Calcium channel blockers, Diuretics and Beta blockers.

Common chromosomal disorders

Chromosomal disorders are caused by changes in the number or structure of chromosomes.

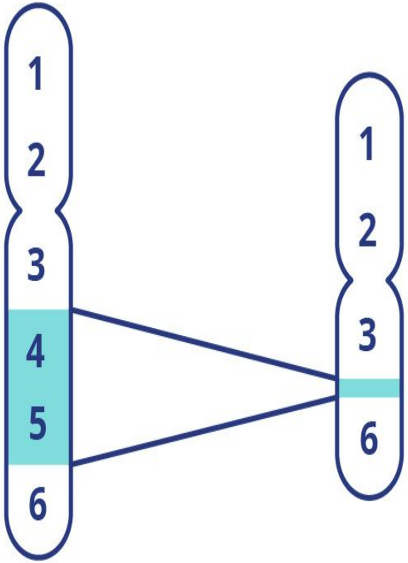
Chromosomal abnormalities can fall under two categories:

1. Structural abnormalities (e.g. deletions or rearrangements)
2. Abnormalities of chromosomal number.

- Abnormalities of chromosomal number generally arise from meiotic non-disjunction (failure of chromosome pairs to separate during cell division) or through anaphase lag (loss of chromosome durring cell division)

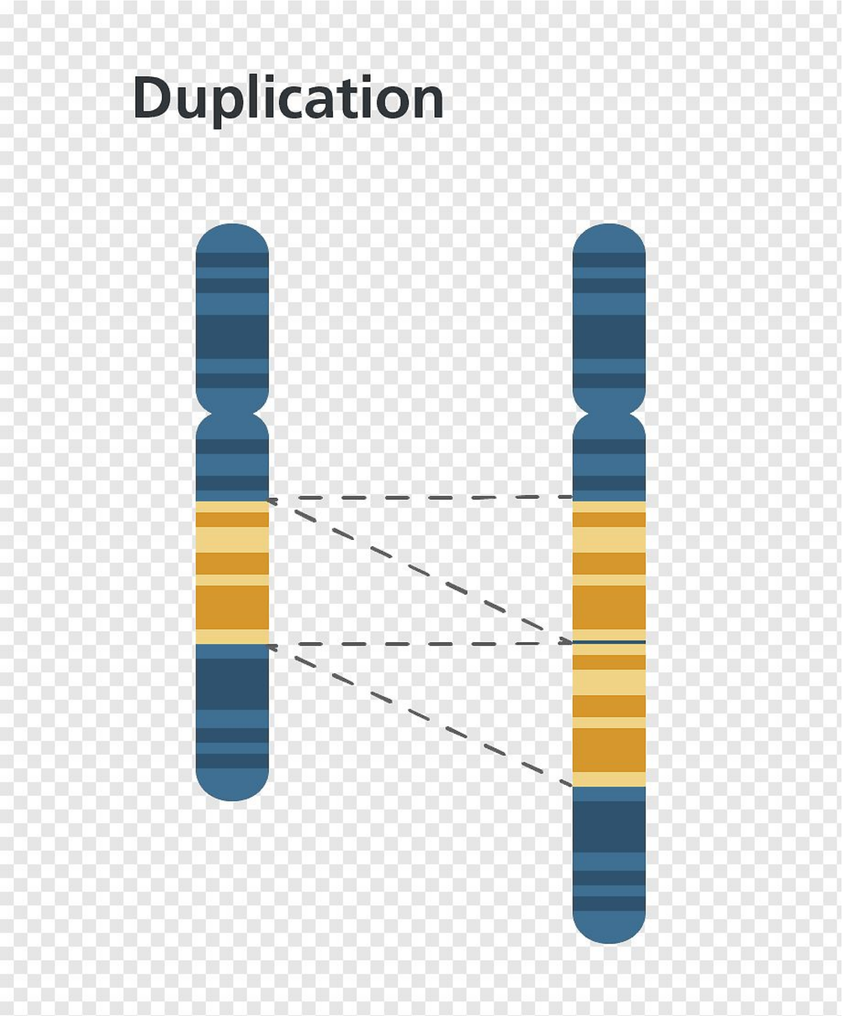
Structural abnormalities can occurs due to several forms;

- **Deletion**, mutation cause part of chromosome to be missing



Cont..

- **Duplication**, mutation cause part of chromosome to be repeated, resulting in extra genetic material



- **Translocation**; mutation can cause one portion of chromosome to be moved to different part of chromosome. These can be categorized into

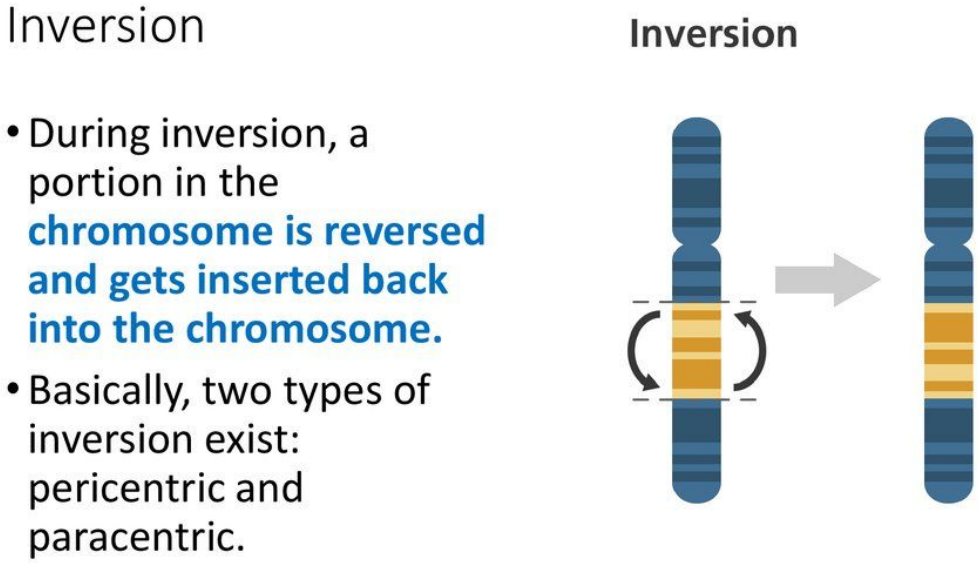
a)Reciprocal translocation; segments from two different chromosomes are exchanged.

b)Robertsonian ; an entire chromosome attaches to another chromosome (Loss of chromosomal segment).

Eg. Chronic myelogenous leukemia inwhich a piece of chromosome 9 breaks off and attaches to chromosome 22

Cont…

- **Inversion**; a mutation resulting in portion of chromosome being in opposite oriented.



Inversion

- During inversion, a portion in the **chromosome is reversed and gets inserted back into the chromosome.**
- Basically, two types of inversion exist: pericentric and paracentric.

Examples of chromosomal disorders

Cri du Chat Syndrome

Cause

- Caused by partial **deletion of chromosome 5p**.

Characteristics

- Patients exhibit a high-pitched cat-like cry at birth, which is usually due to structural abnormalities in the larynx
- Patients also have severe developmental delay and cognitive deficits
- Distinctive facial abnormalities (round face, low-set ears, microcephaly, and a hypoplastic nasal bridge).

continuation

Prader-Willi syndrome and Angelman syndrome

Cause

- Both diseases are due to an identical **deletion on chromosome 15q** and demonstrate imprinting, a phenomenon in which the same mutation results in different phenotypes depending on whether the mutated chromosome was of maternal or paternal origin.
- *Prader-Willi syndrome develops when the deletion is on the paternally derived chromosome,*
- *Angelman syndrome develops when the deletion is on the maternally derived chromosome*.

Characteristics

- Prader-Willi syndrome: Mental retardation; hypogonadism; hypotonia; obesity leading to diabetes.
- Angelman syndrome: “Happy puppet” with ataxic gait and inappropriate laughter; mental retardation; seizures

Cont…

DiGeorge Syndrome

Cause; deletion of long arm of chromosome 22 (22q11 deletion)

Characteristics

- Heart defect
- Cleft palate
- Distint facial feautures including small, low – seat ears, short width eye openings
- Learning , behavooral and mental health problems

Cont…

- **TRISOMY 21 –Down’s syndrome**

Trisomy 21 (also known by the karyotype 47,XX,+21 for females and 47,XY,+21 for males) is caused by a failure of the 21st chromosome to separate during egg or sperm development (nondisjunction) as a result, a sperm or egg cell is produced with an extra copy of chromosome 21; this cell thus has 24 chromosomes. • When combined with a normal cell from the other parent, the baby has 47 chromosomes, with three copies of chromosomes.

Cont…

Characteristics

- Severe mental retardation;
- Duodenal and esophageal atresia
- Specific facial features include flat face; epicanthal folds; wide-set eyes; Brushfield spots (white spots on periphery of iris).
- Congenital heart defects: Endocardial cushion defects leading to ostium primum atrial septal defects, ventricular septal defects, and atrioventricular valve malformations

Cont…

- **TRISOMY 18-Edward’s syndrome**

Edwards' syndrome is a chromosomal abnormality characterized by the presence of an extra copy of genetic material on the 18th chromosome, either in whole (trisomy 18) or in part (such as due to translocations).

- ➢Trisomy 18 (47,XX,+18) is caused by a meiotic nondisjunction in a gamete (i.e., a sperm or egg cell) is produced with an extra copy of chromosome 18; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo has 47 chromosomes, with three copies of chromosome 18

Cont…

Characteristics

- Heart defect
- Clenched hand
- Small jaw
- Overlapping fingers

Cont…

Klinefelter syndrome

Cause

- This disorder is characterized by **two or more X chromosomes with one or more Y** chromosomes (most commonly 47, XXY karyotype with a single Barr body) and is most commonly caused by maternal meiotic nondisjunction.

Characteristics

- Small atrophic testes; tall stature; lack of secondary male characteristics and gynecomastia.
- Male infertility, often resulting from reduced spermatogenesis.
- Occasionally associated with mild mental retardation.
- Lab findings: Decreased testosterone levels; increased FSH and LH levels.

cont…

Patau Syndrome

Cause

- Most cases are caused by **trisomy 13** (usually caused by meiotic nondisjunction).
- A few cases are caused by mosaicism, resulting from mitotic nondisjunction of chromosome 13 during embryogenesis or translocation between chromosomes 13 and 14.

Characteristics

- Severe mental retardation;
- microcephaly and holoprosencephaly;
- cleft lip and palate and microphthalmia (small eyes);
- polydactyly;
- congenital heart and renal defects;

cont…

Turner syndrome

Cause

- Caused by partial or complete **monosomy of the X chromosome** (XO karyotype with no (Barr body).

Characteristics

- Short stature with a broad chest and widely spread nipples;
- Cystic hygroma of the neck, leading to webbed-neck appearance; lymphedema of extremities; coarctation of the aorta and other congenital heart defects.
- Reproductive symptoms include primary amenorrhea, replacement of ovaries with fibrous strands (no ova or follicles), and infantile genitalia and breasts.
- Lab findings: **Decreased estrogen production; increased FSH and LH levels**.

Cont…

- Trisomy X

Also known as 47,XXX . Is a genetic condition inwhich females have extra X chromosome resulting into three X chromosome instead of two.
This condition occurs in approximately 1 in 1000 female births.

Characteristics

- Experience developmental delays, behavioural or emotional challenges
- Tall stature
- Delayed puberty

Single gene disorders

- Single gene disorder is also termed as monogenic disorder
- It is a condition that is caused by mutation in a single gene
- Single gene disorders follow Mendelian pattern of inheritance

Common single gene disorders

CYSTIC FIBROSIS

- CF is an autosomal recessive disease caused by mutations in the CFTR gene encoding the CF transmembrane regulator.
- The principal defect is of chloride ion transport, resulting in high salt concentrations in sweat and in viscous luminal secretions in respiratory and gastrointestinal tracts.
- CFTR mutations can be severe (ΔF508), resulting in multisystem disease, or mild, with limited disease extent and severity

Cont…

- Cardiopulmonary complications constitute the most common cause of death; pulmonary infections and right sided heart failure.
- Pancreatic insufficiency is extremely common; infertility caused by congenital bilateral absence of vas deferens is a characteristic finding in adult patients with CF.
- •Liver disease, including cirrhosis, is increasing in frequency as life expectancy increases.
- Molecular therapies that enhance the transport or stability of mutant CFTR protein are useful in patients who harbour certain CFTR alleles..

Familial hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant disorder caused by mutations in the gene encoding the LDL receptor. Activating mutations of PCSK9 (far less common), which degrades LDL receptors, also cause a similar phenotype.

- Patients develop hypercholesterolemia as a consequence of impaired transport of LDL into the cells.
- In heterozygotes, elevated serum cholesterol greatly increases the risk of atherosclerosis and resultant coronary artery disease; homozygotes have an even greater increase in serum cholesterol and a higher frequency of ischemic heart disease. Cholesterol also deposits along tendon sheaths to produce xanthomas

phenylketonuria

- PKU is an autosomal recessive disorder caused by a lack of the enzyme phenylalanine hydroxylase and a consequent inability to metabolize phenylalanine.
- Clinical features of untreated PKU may include severe mental retardation, seizures, and decreased pigmentation of skin, which can be avoided by restricting the intake of phenylalanine in the diet.
- Female patients with PKU who discontinue dietary treatment can give birth to children with malformations and neurologic impairment resulting from transplacental passage of phenylalanine metabol

Principles of diagnosis of genetic diseases

Doctors use a variety of methods to diagnose genetic disorders. These methods can help identify the specific gene or genes that are causing a person's condition.

Here are the main steps involved in diagnosing a genetic disorder:

Talking about family history: Doctors will ask about your family medical history to see if there are any patterns or potential genetic predispositions.

Checking for physical signs: Doctors will perform a physical examination to look for any physical characteristics or abnormalities that may be associated with a genetic disorder.

Ordering tests: Doctors may order genetic testing, such as DNA sequencing or chromosomal analysis, to identify specific genetic mutations or abnormalities.

Cont…

In addition to these core steps, doctors may also use other methods to diagnose genetic disorders:

Measuring protein levels: Doctors may measure the levels of certain proteins or other substances in the body to help diagnose certain genetic disorders.

Testing pregnant women: For pregnant women, tests like amniocentesis or chorionic villus sampling can be used to diagnose genetic disorders in the developing fetus.

Using imaging scans: Imaging tests such as ultrasound, MRI, or CT scans can help identify physical abnormalities that may be associated with a genetic disorder.

Screening newborns: Newborn screening tests can detect certain genetic disorders shortly after birth, allowing for early intervention and treatment.

Conclusion

Genetic disorders can be a serious challenge for individuals and families.

However, there are many resources available to help people with genetic disorders and their families.

With early diagnosis and treatment, many people with genetic disorders can live healthy and fulfilling lives.